Quantifying cognitive decrements caused by cranial radiotherapy.

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Public Summary:
With the exception of survival, cognitive impairment stemming from the clinical management of cancer is a major factor dictating therapeutic outcome. For many patients afflicted with CNS and non-CNS malignancies, radiotherapy and chemotherapy offer the best options for disease control. These treatments however come at a cost, and nearly all cancer survivors (~11 million in the US alone as of 2006) incur some risk for developing cognitive dysfunction, with the most severe cases found in patients subjected to cranial radiotherapy (~200,000/yr) for the control of primary and metastatic brain tumors. Particularly problematic are pediatric cases, whose long-term survival plagued with marked cognitive decrements results in significant socioeconomic burdens. To date, there are still no satisfactory solutions to this significant clinical problem. We have addressed this serious health concern using transplanted stem cells to combat radiation-induced cognitive decline in athymic rats subjected to cranial irradiation. Animals engrafted with hNSCs exhibit significant improvements in cognitive function. The cognitive benefits derived from engrafted human stem cells suggest that similar strategies may one day provide much needed clinical recourse to cancer survivors suffering from impaired cognition.

Scientific Abstract:
With the exception of survival, cognitive impairment stemming from the clinical management of cancer is a major factor dictating therapeutic outcome. For many patients afflicted with CNS and non-CNS malignancies, radiotherapy and chemotherapy offer the best options for disease control. These treatments however come at a cost, and nearly all cancer survivors (~11 million in the US alone as of 2006) incur some risk for developing cognitive dysfunction, with the most severe cases found in patients subjected to cranial radiotherapy (~200,000/yr) for the control of primary and metastatic brain tumors(1). Particularly problematic are pediatric cases, whose long-term survival plagued with marked cognitive decrements results in significant socioeconomic burdens(2). To date, there are still no satisfactory solutions to this significant clinical problem. We have addressed this serious health concern using transplanted stem cells to combat radiation-induced cognitive decline in athymic rats subjected to cranial irradiation(3). Details of the stereotaxic irradiation and the in vitro culturing and transplantation of human neural stem cells (hNSCs) can be found in our companion paper (Acharya et al., JoVE reference). Following irradiation and transplantation surgery, rats are then assessed for changes in cognition, grafted cell survival and expression of differentiation-specific markers 1 and 4-months after irradiation. To critically evaluate the success or failure of any potential intervention designed to ameliorate radiation-induced cognitive sequelae, a rigorous series of quantitative cognitive tasks must be performed. To accomplish this, we subject our animals to a suite of cognitive testing paradigms including novel place recognition, water maze, elevated plus maze and fear conditioning, in order to quantify hippocampal and non-hippocampal learning and memory. We have demonstrated the utility of these tests for quantifying specific types of cognitive decrements in irradiated animals, and used them to show that animals engrafted with hNSCs exhibit significant improvements in cognitive function(3). The cognitive benefits derived from engrafted human stem cells suggest that similar strategies may one day provide much needed clinical recourse to cancer survivors suffering from impaired cognition. Accordingly, we have provided written and visual documentation of the critical steps used in our cognitive testing paradigms to facilitate the translation of our promising results into the clinic.